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THE "KINDERKREBS IN DER UMGEBUNG VON KERNKRAFTWERKEN" STUDY: RESULTS PUT INTO PERSPECTIVE

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A German case–control study on leukaemia in children below 5 y of age near nuclear installations showed a trend of increasing risk with decreasing distance of place of residence from the sites. The radiation exposure from the sites is considered as being too low by a factor of at least 1000 to explain the observed effect, but little is known about radiation effects from pre- or postnatal exposures on the leukaemia risk for ages up to 4 y. Within the study, it was shown that the observed trend in risk decreases over time. That could be indicative of some agent being involved for which the prevalence is reduced over time. Previous ecological studies showed increased risks among the youngest age groups in the closest vicinity of the sites, but no elevated risks for children of all ages (0–14). This could implicate a shift towards an earlier onset of the disease.

INTRODUCTION

In January 2008, the results from a German case–control study on childhood cancer near nuclear installations were published[1,2]. The study was initiated and funded by the Federal Office for Radiation Protection on behalf of the Federal Ministry for the Environment and conducted by the German Childhood Cancer Registry. An external Experts Group gave advice on study design and data analysis. This paper describes the main characteristics of the study, presents results with respect to childhood leukaemia and attempts to put the results into perspective compared with other findings. All results from the case–control study were taken from Kaatsch *et al.*[1]

THE KINDERKREBS IN DER UMGEBUNG VON KERNKRAFTWERKEN (KiKK) STUDY

The study was designed to test the following null hypotheses: there is no correlation between the proximity of the place of residence to a nuclear power plant (NPP) and cancer risk among children below the age of five. There is no negative trend of risk with distance.

A secondary question of the study was: can an elevated risk be observed within a 5 km distance from the sites?

The study area was defined as the vicinity of 16 nuclear sites with altogether 22 nuclear power stations, i.e. there can be more than one power station at one site. For each site, the two neighbouring districts were defined as the study area plus the next district to the east as a reflection of the prevailing westerly winds in Germany. Due to some overlap of the districts around the single sites, the study area consisted of 41 districts.

Cases were children registered at the German Childhood Cancer Register, which started operations in 1980[3]. The selection of cases was restricted to those diagnosed before 5 y of age and who had been diagnosed between 1980 and 2003. Three population-based controls per case were randomly selected from the files of the registration offices. They were individually matched by age and gender. The controls had to live in the surroundings of the same nuclear site as the reference case at the time of the case's diagnosis.

For the entire study, the following diagnostic groups were used: all cancers, all leukaemias, acute lymphoblastic leukaemia (ALL), acute non-lymphoblastic leukaemia (ANLL), central nervous system tumours and all embryonic cancers other than medulloblastoma. Only the results for leukaemias will be presented here.

Based on 593 leukaemia cases and 1766 controls, the study showed a statistically significant negative trend of increasing leukaemia risk with decreasing distance from the site. The regression parameters for all leukaemias together as well as for ALL and ANLL are shown in Table 1.

For the same diagnostic groups, categorical analyses were also conducted. The categories were the inner 5 and 10 km circles compared with the respective remainder. This shows that previous studies mostly looked at rings and circles of distance, but did not use distance as a continuous variable. The results from the categorical analyses are shown in Table 2. It is important to mention that during the entire study period of 24 y, 37 cases occurred within the 5 km circles around the sites.

Next to the categorical analyses presented in Table 2, a comparison can be made for the odds

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ratios in different categories of distance. Based on the data presented in Kaatsch *et al.*[1], Table 3 shows that for the 5 km distance the regression analysis gives a smaller odds ratio than the categorical analysis. For the 5–10 km distance, the results are the other way around, and after that they are more or less comparable.

Another finding was that for three subsequent study periods there seems to be a decrease in the odds ratios within the 5 km distance. For the period 1980–90, the odds ratio was three (with a lower 95% confidence interval (CI) of 1.54). For periods 1991–95 and 1996–2003, the odds ratios were 2.10 (1.04) and 1.78 (0.99), respectively. The time periods were chosen based on previously conducted ecological studies[4,5]. The period 1996–2003 was not covered by the previous ecological studies.

DISCUSSION

The study consisted of two parts, the second of which was designed to include other risk factors that might probably explain the result. This part of the study was briefly summed up in Spix *et al.*[2]; more detailed information was taken from the study report of Kaatsch *et al.*[6] Telephone interviews were conducted for a subset of cases and controls, i.e. those diagnosed between 1993 and 2003. For all leukaemias, the regression coefficient was found to be 0.44 with a lower 95% CI of −1.86. This is based on 237 cases and 463 controls. There was a strong self-selection in this part of the study. Among cases and controls, the response within the 5 km circle was lower than outside, and this effect was less pronounced among the controls. Thus, as defined in advance, possible confounders found in Part 2 were not to be used as an explanation for the results of Part 1. Still, it is possible to have a look at Part 2 of the study separately. The possible confounders were grouped into the following five groups: socio-economic status, radiation exposure from sources other than from the NPPs, further risk factors mentioned in the literature, child's immunological situation and others. Based on the information for 251 leukaemia cases and 487 controls, no change in estimate was found[6].

Table 1. Regression coefficient for risk by 1/distance[1].

Diagnostic group	β	Lower 95% CI	Cases	Controls
All leukaemias	1.75	0.65	593	1766
ALL	1.63	0.39	512	1523
ANLL	1.99	−0.41	75	225

The author is aware of only one other case–control study that looked into risk based on distance from a nuclear site. This was a study by Gardner *et al.* in relation to the Seascale cluster near the Sellafield reprocessing plant[7]. Here, a comparable trend with 1/distance was described, but the diagnostic entities are different as are the age groups. Further, the trend was based on the inner 5 km circle, where there existed a known cluster. In the second German ecological study[5], the result was highly dependent on a leukaemia cluster around the Northern German NPP Kruemmel[8,9], which is persistent over time[10]. To test whether the result of the KiKK study is dominated by one single site, the analysis was repeated by omitting one site at a time. The trend of an increasing risk with decreasing distance could always be observed, i.e. even when excluding the Kruemmel site from the analysis[1].

As stated above, a decreasing trend of odds ratios over time within the 5 km circle has been observed in the German case–control study. This trend raises the question whether there might be an active agent the prevalence of which decreases over time. Whether this agent is related to the NPPs can only be answered when results are available from periods prior to the start up of the plants. Results from the UK show that there is no hint of a difference in the leukaemia rates before and after start up of nuclear installations[11].

There is a large body of evidence that the risk of childhood leukaemia among the 0–4 y olds increases when exposure to 50/60 Hz electromagnetic fields from power lines exceeds 0.3 μT (see Ahlbom, this issue).[12] Exposures from the power lines near the NPPs might be considered to be a

Table 2. Results for 5 and 10 km distance categories[1].

Diagnostic group	Distance	OR	Lower 95% CI	Cases
All leukaemias	≤5 km versus >5 km	2.19	1.51	37
	≤10 km versus >10 km	1.33	1.06	95
ALL	≤5 km versus >5 km	1.98	1.33	30
	≤10 km versus >10 km	1.34	1.05	84
ANLL	≤5 km versus >5 km	3.88	1.47	7
	≤10 km versus >10 km	1.30	0.66	10

Table 3. Comparison of odds ratios for different categories of distance, as derived from regression and categorical analysis (based on Kaatsch *et al.* [1]).

Distance	Odds ratios (based on regression analysis)	Odds ratios (based on categorical analysis)
<5 km	1.76	2.27
5– < 10 km	1.26	1.09
10 – < 30 km	1.10	1.01
30– < 50 km	1.05	1.11
50– < 70 km	1.03	0.90
70+ km	1.02	1.00 (reference)

Table 4. Odds ratios for different time periods as derived from previous ecological studies and the case–control study[1].

Study period	Ecological study RR and 95% CI	Case–control study OR and one-tailed lower 95% Cl
1980–90	3.01 (1.25;10.3)	3.00 (1.54)
1991–95	1.39 (0.69;2.57)	2.10 (1.04)
1996–2003		1.78 (0.99)
1980–95	1.49 (0.98;2.20)	2.53 (1.57)
1980–2003		2.19 (1.51)

confounder, but the power lines only cover narrow corridors and are built mostly on agricultural areas rather than in populated areas.

Finally, the current results have to be compared with those from ecological studies. In Table 4, the new results are compared with those from the previous ecological studies in Germany. It is interesting that for the period 1980–90 both types of studies lead to the same result though the design of the ecological study[5] was criticised as being biased towards overestimating the risk. These criticisms were taken into account in the design of second study[5]. Table 4 shows that the point estimates for the relative risks are below those derived from the case–control study when looking at the time periods 1991–95 and 1980–95.

But assuming that there is no ecological fallacy, all studies showed elevated risks among the youngest age group and in the closest vicinity. Taking all internationally available studies together, there seems to be no increased leukaemia risk for all children below the age of 15[13–15]. Thus, an elevated risk among 0–4 y old would mean a lower risk among the 5–14 y old. That is exactly what can be seen based on German data[16]. For children below the age of five, the relative risk within a 15 km distance from the nuclear sites under study is 1.31. For the three categories below 5, 5–10 and 10–15 km, the values are 2.87, 1.15 and 0.52, respectively, and only the value of 2.87 is statistically significant. Does that mean that an, as yet undefined, agent causes an earlier onset of the disease close to the sites among vulnerable children who would otherwise have come down with leukaemia later? If so, this would explain the absence of additional cases among all children.

Another point that has to be considered is the results regarding the risks near potential sites. There are two studies available[16,17], but only in one[16] can results for young children in the closest vicinity of these sites be studied. Again, for the time period 1980–95, the risk is elevated. The relative risk is 3.82, though not statistically significant.

On the basis of current knowledge on radiation risk, the radiation exposure to the public has to be considered as being too low by a factor of at least 1000 to explain the observed effect. A review of the risk of childhood cancer following antenatal and postnatal radiation by Wakeford[18] indicated that increased risks are observed following antenatal X-ray exposures, but no risks are observed for postnatal exposures. This study examined risk up to the age of 14. It has to be kept in mind that little is known about radiation effects from antenatal exposures or those during infancy on leukaemia risk for ages up to 4 y.

Overall, what are possible explanations for the German findings? Is it radiation at low exposures with a high risk at young ages? Is it the combined effects of radiation? If so, the following questions have to be answered: which factors are involved? What is the total risk? What is the contribution of radiation? If radiation is not involved, which potential risk factors are characterised by the observed distance from a site? A proportion of these questions can probably be answered by the various analyses that have been conducted as a part of the activities of the British Committee on Medical Aspects of Radiation in the Environment (COMARE). COMARE has recently published its 11th report[19]. Further experience is available in France[20]. Any further investigations as a follow-up of the KiKK-study findings have to take these experiences into account and define in advance which questions are left open.

In their report on the first large study in England and Wales on cancer mortality near nuclear installations, Forman *et al.* stated some 20 y ago: 'it is, therefore, necessary to consider carefully whether each of the positive results may be due to chance, or to socio-economic/environmental differences, or to the direct presence of the installations'[21]. These considerations are still valid. The KiKK study points in the direction of the 'presence of the installations', but clearly no explanation for a causal relation between any chemical or physical risk factor and the observed risk is possible based on the KiKK-study results.

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